that SLPs will be used in early stage disease when the spontaneous clearance rate is still high. Similarly, due to the need for local imiquimod treatment in the case of TA-CIN treatment, tolerability is a significant issue as the majority of women experience local and systemic side effects lasting for the duration of imiquimod treatment, which may affect daily activities.

[0011] A possible alternative is to use nucleic acid based vaccination such as DNA vaccines or viral vaccines encoding the HPV E6 and/or E7 protein for vaccination.

[0012] However, the HPV E6 and E7 proteins have oncogenic potential and thus vaccination with vaccines that comprise nucleic acids encoding these proteins poses a risk of inducing cellular transformation due to the possibility of prolonged expression of the antigens.

[0013] Therefore, in case of genetic vaccination, non-oncogenic/detoxified versions of E6 and/or E7 can be used in order to exclude any risk of cellular transformation due to the vaccination. Loss of oncogenic potential of wild-type E6 and E7 is commonly achieved by deletion and/or substitution of residues known to be important for the function of these proteins (e.g., Smahel et al., 2001, *Virology* 281:231-38; Yan et al., 2009, *Vaccine* 27:431-40; Wieking et al., 2012, *Cancer Gene Ther.* 19:667-74; WO 2009/106362). However, a disadvantage of these approaches is that they carry the risk of removing important T-cell epitopes from and/or introducing new undesired T-cell epitopes into the proteins, and may thus not lead to the desired immune response.

[0014] In an alternative strategy to remove the oncogenic potential of HPV16 E6 and E7, shuffled versions (i.e., polypeptides wherein fragments of the wild-type protein are re-ordered) of the E6 and E7 proteins have been constructed (e.g., Ohlschlager et al., 2006, *Vaccine* 24:2880-93; Oosterhuis et al., 2011, *Int. J. Cancer* 129:397-406; Oosterhuis et al., 2012, *Hum. Gen. Ther.* 23:1301-12). However, these approaches would still require manufacturing, formulation and administration of multiple molecules to ensure inclusion of all possible epitopes of both the E6 and E7 proteins, resulting in sub-optimal logistics and relatively high costs, and moreover the strategies described introduce potentially strong non-natural epitopes that are not present in E6 and E7 and since immune responses could be diverted from relevant E6/E7 epitopes toward such non-natural epitopes, the described constructs may not have the optimal immunological characteristics.

[0015] Thus, there remains a need in the art for therapeutic vaccines against HPV, preferably having less of the drawbacks of the approaches described before.

BRIEF SUMMARY

[0016] Provided are nucleic acid molecules that encode polypeptides that comprise essentially all possible T-cell epitopes of HPV16 oncoproteins E6 and E7, but nevertheless have a strongly reduced (as compared to wild-type ("wt") E6 and E7), up to non-detectable, transforming activity, by comprising fragments of the E6 and E7 proteins that have been re-ordered, while at the same time containing a minimized number of undesired neo-epitopes. This is in contrast to molecules previously presented by others.

[0017] Described is a nucleic acid molecule encoding a polypeptide comprising a sequence as set forth in SEQ ID NO:1.

[0018] The encoded polypeptide may further comprise a leader sequence.

[0019] In certain embodiments, the encoded polypeptide further comprises at least one epitope of a human papillomavirus (HPV) E2 protein, for example, an HPV16 E2 protein. The E2 protein may be mutated to decrease DNA binding, e.g., by a deletion or mutation(s) in its DNA binding domain. In certain embodiments, the encoded polypeptide comprises a sequence as set forth in SEQ ID NO:3 or SEQ ID NO:5.

[0020] In certain embodiments, the nucleic acid sequence is codon-optimized, e.g., for expression in human cells.

[0021] In certain embodiments, the nucleic acid molecule comprises a polynucleotide as set forth in SEQ ID NO:2, SEQ ID NO:4 , or SEQ ID NO:6.

[0022] Also provided is a vector comprising a nucleic acid molecule as described herein, wherein the molecule encoding the polypeptide is operably linked to a promoter.

[0023] In certain embodiments, the vector is a DNA vector such as a plasmid. In other embodiments, the vector is a viral vector, such as an MVA vector or a recombinant adenoviral vector. In certain preferred embodiments, the vector is a recombinant adenovirus.

[0024] In certain embodiments, the promoter in the vector is operably coupled to a repressor operator sequence, to which a repressor protein can bind in order to repress expression of the promoter in the presence of the repressor protein. In certain embodiments, the repressor operator sequence is a TetO sequence or a CuO sequence.

[0025] Also provided is a vaccine composition comprising a vector as described herein, and a pharmaceutically acceptable excipient.

[0026] Also provided is a method of inducing an immune response against HPV, in particular HPV16, in a subject, the method comprising administering to the subject a vaccine composition as described herein. Also provided is a vaccine as described herein for use in inducing an immune response against HPV, in particular HPV16.

[0027] In certain embodiments, the vaccine is administered to the subject more than once.

[0028] Also provided is a method for treating any of: persistent HPV infection (in particular persistent HPV16 infection), vulvar intraepithelial neoplasia (VIN), cervical intraepithelial neoplasia (CIN), vaginal intraepithelial neoplasia (VaIN), anal intraepithelial neoplasia (AIN), cervical cancer (such as cervical squamous cell carcinoma (SCC), oropharyngeal cancer, penile cancer, vaginal cancer, and/or anal cancer in a subject, the method comprising administering to the subject a vaccine as described herein. Also provided is a vaccine as described herein for use in treatment of any of: persistent HPV infection (in particular persistent HPV16 infection), vulvar intraepithelial neoplasia (VIN), cervical intraepithelial neoplasia (CIN), vaginal intraepithelial neoplasia (VaIN), anal intraepithelial neoplasia (AIN), cervical cancer (such as cervical squamous cell carcinoma (SCC), oropharyngeal cancer, penile cancer, vaginal cancer or anal cancer in a subject.

[0029] Also provided is a polypeptide comprising a sequence as set forth in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:5.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] FIG. **1**: Expression of fusion proteins of HPV16 E6 and E7. HEK-293T cells were transiently transfected with